

Attorney Docket No.:

DEX-0115

Inventors:

Salceda et al.

Serial No.:

09/717,883

Filing Date:

November 21, 2000

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REMARKS

Claims 1-16 are pending in the instant application. Claims 1, 2 and 8-16 have been withdrawn from consideration by the Examiner. Claims 3-7 have been rejected. Claim 3 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Restriction Requirement

The Examiner has made a Restriction Requirement as follows:

Group I, claims 1-2, drawn to a diagnostic marker comprising Ovr107, classified in class 536, subclass 24.31;

Group II, claims 3-7, drawn to a method of diagnosing, staging and monitoring cancer, classified in class 435, subclass 4;

Group III, claim 8, drawn to a method of identifying therapeutic agents for imaging and treating cancer, classified in class 435, subclass 7.1;

Group IV, claim 9, drawn to an antibody to Ovr107, classified in class 424, subclass 138.1;

Group V, claims 10-11, drawn to a method of imaging cancer, classified in class 424, subclass 9.3;

Group VI, claims 12-14, drawn to a method of treating cancer, classified in class 424, subclass 183.1;

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Group VII, claim 15, drawn to a method of inducing an immune response, classified in class 424, subclass 184.1; and

Group VIII, claim 16, drawn to a vaccine comprising Ovr107, classified in class 424, subclass 184.1.

The Examiner suggests that these Groups are distinct. Specifically, with respect to Groups I and IV and II, V-VI, the Examiner has acknowledged the Groups to be related as product and process of use. However, the Examiner suggests that the products can be used for a number of different processes and that the processes can be performed with a number of different products. With respect to Groups I and IV, the Examiner suggests that the claims are drawn to structurally and functionally different molecules. With respect to Groups II, and V through VII, the Examiner suggests that the methods differ in steps, mode of operation, reagents needed and serve different endpoints and effects.

Applicants respectfully traverse this restriction requirement.

MPEP §803 provides two criteria which must be met for a restriction requirement to be proper. The first is that the inventions be independent or distinct. The second is that there would be a serious burden on the Examiner if the restriction is not required. A proper search of the prior art relating to Ovr107 as

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used in the claims of Group II, should also reveal art relating to the diagnostic marker itself, as set forth in Group I, additional uses for the marker as set forth in Groups III, VII and VIII, as well as antibodies against this marker and methods of using these antibodies as set forth in Groups IV, V and VI. Thus, it does not appear that a serious burden would be placed upon the Examiner if restriction were not made.

Accordingly, since this Restriction Requirement does not meet both criteria as set forth in MPEP § 803 to be proper, it is respectfully requested that this Restriction Requirement be withdrawn.

However, in an earnest effort to be completely responsive, Applicants elect to prosecute Group II, claims 3-8, with traverse.

II. Objection to Abstract

The Examiner has objected to the Abstract as not being in compliance with 37 C.F.R. 1.72(b). Accordingly, in an earnest effort to advance the prosecution of this case, Applicants are providing a replacement Abstract herewith which has been amended to enable the reader to ascertain quickly the character of the subject matter covered by this disclosure. No new matter has been added by this amendment. Withdrawal of the objection to the Abstract is respectfully requested in light of this amendment.

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III. Rejection of Claims 3-7 under 35 U.S.C. § 112, first paragraph

Claims 3-7 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner has listed several reasons as to why the instant disclosure fails to meet the enablement requirements including: the nature of the invention; the state of the prior art and predictability or lack thereof in the art; the amount of direction and guidance present and the presence or absence of working examples; and the breadth of the claims and the quantity of experimentation needed. More specifically, the Examiner suggests that since it is not known in the art if Ovr107 levels in cells, tissue of bodily fluids may be indicative of cancer when compared to normal, it would be extremely unpredictable to use Ovr107 levels as a method of diagnosis, staging and monitoring of cancer and metastasis. Further, the Examiner suggests that until some "substantial evidence" can be attributed to the claimed method, one of ordinary skill in the art would be required to perform additional experimentation in order to practice the invention as claimed.

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Applicants respectfully traverse this rejection.

MPEP § 2164 sets forth the enablement requirement of 35 U.S.C. § 112, first paragraph. The enablement requirement refers to the requirement of 35 U.S.C. § 112, first paragraph that the specification describe how to make and how to use the invention. The invention that one skilled in the art must be enabled to make and use is defined by the claim(s) of the particular application.

The Examiner states the nature of the invention at page 5, first paragraph, of the Office Action, as follows:

the claimed invention is drawn to a method of diagnosing the presence and metastases of cancer, in addition to staging, and monitoring for onset of metastasis and stage changes, wherein the expression levels of Ovr107 in cells, tissues of bodily fluids in a patient are compared to expression levels in normal human control samples.

Accordingly, the Examiner's concern expressed further at page 5 of the Office Action relating to enablement of "mutant forms of the gene characterized by SEQ ID NO:1 encoding Ovr107" not being disclosed in the specification is misplaced. The claims are not drawn to detecting mutant gene forms of Ovr107 per se. One of ordinary skill would recognize that the assays taught at pages 5-14 of the specification will detect levels of Ovr107 independent of

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the presence or absence of mutations. Similarly, the Examiner's suggestion that the specification fails "to give any biological activity for Ovr107" nor any "art of record disclosing any specific activity for it" is irrelevant since the claimed invention is drawn to detecting the levels of Ovr107 independent of biological activity.

Applicants also respectfully disagree with the Examiner's suggestion that the fact that there is no evidence in the art teaching Ovr107 expression levels and its correlation with cancer, makes it unpredictable to diagnose cancer based on Ovr107 expression. The fact that the prior art does not teach Ovr107 as a diagnostic marker for cancer renders the claimed invention novel and unobvious. However, the absence of prior art teaching a claimed invention does not make the claimed invention unpredictable. As set forth in MPEP § 2164.03, the predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention.

In addition, Applicants respectfully disagree with the Examiner's suggestion that for a diagnosis a systemic comparison and contrasting of the clinical findings is necessary. The claims are not drawn to differential diagnosis wherein a determination of

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which of two or more diseases with similar symptoms is made. Claim 3 is simply drawn to diagnosing, which is defined in Webster's Dictionary as the act or process of deciding the nature of a diseased condition by examination. Clearly, determining levels of Ovr107 in cells, tissues or bodily fluids in a patient as taught in the instant application constitutes an act or process of examination for deciding the nature of a diseased condition.

The Examiner acknowledges at page 5, lines 7-8 of the Office Action that the instant specification discloses the sequence (referring to Ovr107) and "the fact that it is expressed in ovarian and an array of cancers". Further, contrary to the Examiner's suggestion, the specification provides guidance as to what level of Ovr107 expression would constitute abnormal levels and how these levels would be indicative of a disorder. Specifically, at page 7, lines 16 through 22 of the application it is taught that a positive result indicating that the patient being tested has cancer is one in which cells, tissue or bodily fluid levels of Ovr107 are at least two times higher, and most preferably at least 5 times higher, than in preferably the same cells, tissue or bodily fluid of a normal human control. In addition, beginning at page 20 of the instant specification, data are provided evidencing Ovr107 mRNA overexpression in the majority of cancer samples as compared to

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normal in 132 samples in 15 different tissue types. These data are clearly demonstrative of an increase in Ovr107 levels being indicative of cancer.

As evidenced by the review article provided herewith (Berns, A. Nature 2000 403:491-492), gene expression data such as provided in the instant application is used routinely by those of skill in the art to examine activity of a gene under various conditions. Accordingly, one of skill in the art could clearly routinely extrapolate the disclosed results provided in the instant application of an increase in Ovr107 levels being indicative of cancer to the claimed invention.

In an earnest effort to advance the prosecution of this case and in accordance with the teachings at page 7, line 16 through 22 and data provided in the specification beginning at page 20, Applicants have amended claim 3 to clarify that an **increase** in Ovr107 levels is diagnostic of cancer. As discussed in detail above, one skilled in the art is enabled by the instant specification to make and use the claims as amended.

It is therefore respectfully requested that the rejection of claims 3-7 under 35 U.S.C. § 112, first paragraph, be withdrawn.

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IV. Supplemental IDS

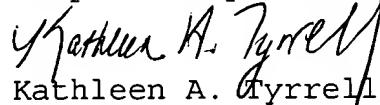
A supplemental IDS and requisite fee are provided herewith.

V. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,


Kathleen A. Tyrrell

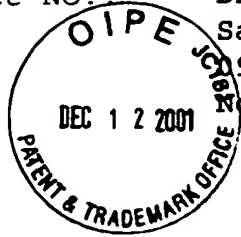
Registration No. 38,350

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend claim 3 as follows:

3. (amended) A method for diagnosing the presence of cancer in a patient comprising:

(a) determining levels of Ovr107 in cells, tissues or bodily fluids in a patient; and

(b) comparing the determined levels of Ovr107 with levels of Ovr107 in cells, tissues or bodily fluids from a normal human control, wherein ~~a change~~ an increase in determined levels of Ovr107 in said patient versus normal human control is associated with the presence of cancer.

sound waves with single-electron quantum waves moving over a flat surface of copper. The speaker is the STM tip held just above the surface and supplying electrons; the frequency of the sound is the energy (and corresponding wavelength, controlled by the voltage applied to the tip) of the electrons; and the walls and furniture are edges or other defects, such as iron atoms set in a particular pattern. Finally, power output in the acoustic case becomes current flow in the STM. The famous STM images are the power map of the region scanned by the tip.

The analogy goes further still — real walls and furniture can absorb sound, and windows may be open, so some of the outgoing sound energy is either absorbed or escapes, making the returning signal weaker. In a typical room the sound bounces only a couple of times before it is negligible. That happens with electrons too: in the classic 'quantum corral' arrangement of, say, 60 iron atoms in a circle, the iron walls reflect only about 25% of the wave back into the cavity.

We can now begin to understand the latest experiments by Eigler's group: Manoharan *et al.*⁴ have created a tiny laboratory for remote sensing, in the form of an elliptical quantum corral a few tens of ångströms across. An ellipse is a remarkable geometric object that perfectly focuses either waves or rays starting at one focus onto the other focus (Fig. 1). Manoharan *et al.* put a cobalt atom at one focus and bombarded it with electrons from an STM tip placed at the other focus. Cobalt has what is called a Kondo resonance at low temperatures. This arises because cobalt has a magnetic moment, which at low temperatures causes the 'Fermi sea' of conduction electrons around it (if it is embedded in a metal such as copper) to become oppositely polarized, thereby screening the magnetic moment and producing a many-body singlet state. This Kondo resonance is observed as a rise in resistance at very low temperatures, as the Kondo clouds form, making the magnetic impurities more effective at scattering conduction electrons.

It was Eigler's original dream to see a Kondo resonance up close and personal. The first STM evidence for a Kondo resonance was seen by Madhavan *et al.*⁶, a group led by M. F. Crommie, who did the original quantum corral work with Eigler and Lutz. (Li *et al.*⁷ saw STM surface Kondo resonances around the same time.) The experiments in an elliptical corral reported by Manoharan *et al.*⁴ add a remarkable twist. The Kondo resonance, which manifests itself as a blip in the conductance if the tip is held just above the cobalt atom, has the same (but attenuated) blip if the tip is at the empty focus of the elliptical corral. This raises several fascinating issues. If a Kondo blip is seen at the remote location, does that mean the electronic structure is perturbed there too? Is the electronic structure really being projected to a

remote place, as the authors claim? Or, like a light bulb at one focus of a mirrored elliptical room, do we just see a light bulb at the other focus (as would happen), only to find out that it's not really there when we try to touch it?

We may get some insight by returning to the acoustic analogy. Suppose at one focus of an elliptical room there is a drum that resonates near some frequency, simulating a Kondo resonance. With the speaker on top of the drum, we find a blip in power supplied near the resonance frequency. If we then put the speaker at the other focus, what will happen as we sweep through that same frequency? This is left as an exercise for the reader, as are any conclusions to

be drawn regarding remote projection. ■

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1. Crommie, M. F., Lutz, C. P. & Eigler, D. *MNature* **363**, 524–527 (1993).
2. Crommie, M. F., Lutz, C. P. & Eigler, D. *MScience* **262**, 218–220 (1993).
3. *Physics Today* November (1993).
4. Manoharan, H. C., Lutz, C. P. & Eigler, D. *MNature* **403**, 512–515 (2000).
5. Heller, E. I., Crommie, M. F., Lutz, C. P. & Eigler, D. *MNature* **369**, 464–466 (1994).
6. Madhavan, V. *et al. Science* **280**, 567–569 (1998).
7. Li, J., Schneider, W.-D., Berndt, R. & Delley, B. *Phys. Rev. Lett.* **80**, 2893–2896 (1998).
8. Weber, E. H. *Wellenlehre: Auf Experimente Gegründet oder über die Wellen Trefbarer Flüssigkeiten mit Anwendung auf die Schall- und Lichtwellen* (Bey Gerhard Fleischer, Leipzig, 1825).

Cancer

Gene expression in diagnosis

Anton Berns

With advances in high-density DNA microarray technology, it has become possible to screen large numbers of genes to see whether or not they are active under various conditions. This is gene-expression profiling, and there has been an expectation that it will revolutionize cancer diagnosis (Box 1)². The thinking is that tumour behaviour is dictated by the expression of thousands of genes, and that micro-array analysis should allow that behaviour and the clinical consequences to be predicted. This rationale is sound enough, but until now it has not been substantiated by experiment.

On page 503 of this issue¹, Alizadeh *et al.* deliver such substantiation. The particular cancer they have looked at is diffuse large B-cell lymphoma (DLBCL), a disease that takes in a clinically and morphologically varied group of tumours that affect the lymph system and blood. The authors carried out gene-expression profiling with a

'Lymphochip', a microarray carrying 18,000 clones of complementary DNA designed to monitor genes involved in normal and abnormal lymphocyte development.

Using clustering analysis, Alizadeh *et al.* could separate DLBCL into two categories, which had marked differences in overall survival of the patients concerned. The gene-expression signatures of these subgroups corresponded to distinct stages in the differentiation of B cells, the type of lymphocyte that makes antibodies.

Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin's lymphoma. With current treatments, long-term survival can be achieved in only 40% of patients. There are no reliable indicators — morphological, clinical, immunohistochemical or genetic — that can be used to recognize subclasses of DLBCL and point to a differential therapeutic approach to patients³.

Expression profiling has already shown its usefulness in identifying genes with high

Box 1: Gene-expression profiling with microarrays

Imagine a 1-cm² chessboard. Instead of 64 squares, it has thousands, each containing DNA from a specific gene. This is a DNA microarray. The activity of each gene on the microarray can be compared in two populations of cells (A and B).

When a gene is expressed it makes a transcript, and the whole population of these products from a cell can be

tagged with a fluorescent dye (say, red for the A cells, green for the B cells). The microarray is bathed in a mixture of the red and green transcripts. Those that originate from a specific gene will bind to that gene on the microarray, turning red, green or somewhere in between, depending on the relative numbers of transcripts in the two cell types.

So the microarray provides

a snapshot of gene activity for thousands of genes. Data from many experiments can be compared and genes that have consistent patterns of activity can be grouped or clustered. In this way, genes that characterize a particular cell state, such as malignancy, can be identified — so providing new information about the biology of the cell state.

Mark Patterson

or low expression levels in specific cell types under defined conditions — for instance, when being stimulated with growth factors or treated with drugs, or when the cell's degree of attachment to the extracellular matrix varies (this last characteristic may determine tumour spread)²⁻⁷. More recently, reports on tumour classification have also begun to emerge. Acute leukaemias can effectively be divided into the lymphoblastic and myeloblastic forms by expression profiling⁸. But in these studies, no multigene-expression signature was found that correlated with a new leukaemia subgroup, or with clinical outcome, in the relatively small group of tumours examined.

In the case of Alizadeh and colleagues' analysis⁹ of DLBCL, the situation is different. Hierarchical clustering of the gene-expression data divided DLBCLs into two groups: one had the signature of B cells from the germinal centres (the B-cell factories in lymph nodes); the other had the signature of activated B cells. The outlook for patients who had tumours with the activated-B-like signature was much worse — 16 out of 21 died, compared with 6 out of 19 patients with the germinal-centre B-cell signature. Importantly, the predictive value was independent of the standard clinical parameters of prognosis, the International Prognostic Indicator.

That is far from the end of the story, of course. As the authors point out, most of the patients in the 'favourable prognosis' group that die do so within the first two years of diagnosis, whereas some of the patients in the 'poor prognosis' group were still alive after five years. The question is whether there is a 'hidden signature' that, if found, would enable early identification of these subgroups. For the moment, we just cannot say. Testing of more tumours, and using larger or different DNA microarrays, might be needed to resolve this question. In addition, some prognostic indicators might escape detection by expression profiling as they are qualitative, rather than quantitative. That is, genetic (allelic) differences might mean that some genes escape expression screening. They could encode proteins with a different activity or stability that affects tumour progression or response to treatment. In this respect, monitoring of single-nucleotide polymorphisms (SNPs — individual differences at a single base pair that mark a particular genetic variation in the population) would constitute an appealing complementary approach to screening⁹.

When more expression signatures of larger tumour sets become available, it will become clear how this approach will improve monitoring of the stages in which tumours grow and spread, and therefore prognosis. The expectations are high. Furthermore, the better definition of patient groups, made possible by expression profiling, is of obvious importance for assessing the efficacy

of various treatments. Patients will benefit directly from the tailoring of therapies to specific subclasses of tumours.

Finally, gene-expression profiling can be used to identify the genes and pathways that really matter for the tumorigenic process, thereby revealing new targets for therapy. The studies discussed here, and others, show that it is indeed feasible to identify such pathways. For example, high expression of the homeobox gene *HOXA9*, previously identified as a potent oncogene, was correlated with the failure to induce remission in a small group of patients suffering from acute myeloblastic leukaemia¹⁰. The DLBCL study revealed the increased expression of a series of genes involved in the inhibition of apoptosis (programmed cell death); this, too, might be a therapeutic avenue to explore.

A word of caution. Prognoses based on gene-expression signatures, and — in the future — SNP analysis, are likely to have their limitations. These methods will probably provide quite reliable predictions of the patient responses to initial therapies. The

question then is how much 'noise' will remain as a result of tumour heterogeneity and genetic instability. Both are hallmarks of most malignancies and can lead to recurrent disease, as cancer specialists and their patients know only too well. Time will tell.

For the moment we are witnessing spectacular developments in tumour diagnosis. These developments are going hand in hand with new treatments targeted to defined regulatory pathways that are frequently deregulated in cancer. So although caution is in order, so too is optimism.

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1. Alizadeh, A. A. et al. *J. Clin. Immunol.* 18, 373–379 (1998).
2. Perou, C. M. et al. *Proc. Natl Acad. Sci. USA* 96, 9212–9217 (1999).
3. Alizadeh, A. A. et al. *Nature* 403, 503–511 (2000).
4. Harris, N. L. et al. *J. Clin. Oncol.* 17, 3835–3849 (1999).
5. Iyer, V. R. et al. *Science* 283, 83–87 (1999).
6. Marton, M. J. et al. *Nature Med.* 4, 1293–1301 (1998).
7. Alon, U. et al. *Proc. Natl Acad. Sci. USA* 96, 6745–6750 (1999).
8. Golub, T. R. et al. *Science* 286, 531–537 (1999).
9. Cargill, M. et al. *Nature Genet.* 22, 231–238 (1999).

Plant ecology

Alien invaders

Peter D. Moore

There are plenty of examples of the ecological mayhem that can result from the human introduction of species into new areas. Stories of goats on Pacific islands, rabbits in Australia and rats in New Zealand are all familiar, as are the world's plant pests, from the aquatic weeds of tropical waterways to the nitrogen-fixing shrubs of Hawaii. The ecological repercussions of plant invasions are often far-reaching, and a fuller understanding of the complexities of ecosystem relationships may provide methods for the control of invasive species. These principles are illustrated by papers in the journals *Conservation Biology* and *Journal of Applied Ecology*. The first deals with the impact of invasive shrubs on songbird breeding success in North America¹; the second with the potential control of unwanted grasses on golf courses in Britain².

Studies of invasive plants often concentrate on the effects of the newcomer on the existing plant community, but its influence may be felt throughout the ecosystem. Schmidt and Whelan¹ have analysed the consequences of the invasion of native North American woodlands by exotic shrubs — a honeysuckle, *Lonicera maackii*, and buckthorn, *Rhamnus catharticus*. Their particular concern was whether these shrubs are used for nesting by woodland songbirds and, if so, whether nest predation in these species differs from that found in

native shrubs and trees. Both of these invasive shrubs are now common in the eastern part of North America, and both proved to be suitable for and attractive to nesting American robins (*Turdus migratorius*; Fig. 1)



Figure 1 The American robin (*Turdus migratorius*), painted by J. J. Audubon. Schmidt and Whelan¹ found that the robins' nests were more vulnerable to predation when sited in the invading honeysuckle *Lonicera maackii* than in native trees and shrubs.